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THE 2012 ACCF/AHA FOCUSED UPDATE OF THE UNSTABLE ANGINA/NON-ST-ELEVATION MYOCARDIAL INFARCTION (UA/NSTEMI) GUIDELINE: A CRITICAL APPRAISAL

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Introduction

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) recently published the 2012 ACCF/AHA Focused Update of the Guidelines for the Management of Patients with Unstable Angina and Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline and Replacing the 2011 Update).[1] These guidelines were developed in collaboration with multiple societies and represent an important landmark in the management of patients with unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI). This paper provides a critical overview of some of the clinically relevant novel and modified recommendations proposed by the updated guideline.

Oral Antiplatelet Therapies

Prasugrel

Prasugrel was incorporated into the 2012 focused update[1] following the results of the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction (TRITON-TIMI 38)[2] and its subsequent FDA approval in July 2009. Like clopidogrel, prasugrel is an irreversible inhibitor of the $P2Y_{12}$ receptor; however, it has quicker onset of action (within 30 minutes), achieves greater inhibition of adenosine diphosphate-induced platelet aggregation, and is associated with lesser variability related to drug metabolism or genetic pleomorphism.

TRITON-TIMI 38[2] was a pivotal randomized controlled trial that evaluated the efficacy of prasugrel versus clopidogrel in 13,608 moderate- to high-risk patients with acute coronary syndrome (ACS). The trial demonstrated a 19% significant reduction in the composite of cardiovascular death, MI, or stroke with prasugrel (60-mg loading followed by 10-mg daily doses) compared with clopidogrel at a mean of 15-months follow-up. This salubrious outcome was driven by a reduction in nonfatal MI, was observed as early as 3 days post-randomization, and was accompanied by a reduction in urgent target vessel revascularization (TVR) and stent thrombosis (ST) in the prasugrel group.[2] The benefits of prasugrel versus clopidogrel were tempered by an increase in non-CABG TIMI major bleeding events (the key safety endpoint) (2.4% vs. 1.8%; $P = 0.03$), including more life-threatening and fatal bleeding events. Despite an overall 32% increase in major bleeding with prasugrel, the net clinical-benefit endpoint still favored prasugrel,[2] with stronger benefits observed in high-risk patients such as diabetics.

Jneid et al.[1] recommended the use of prasugrel as an alternative to clopidogrel in ACS patients undergoing percutaneous coronary intervention (PCI), cautioned against its use in those with a history of stroke or transient ischemic attack because of observed net clinical harm (as shown previously[3]), and recommended its empiric discontinuation at least 7 days before planned CABG (Table 1). It is important to note that TRITON-TIMI 38 enrolled ACS patients scheduled to undergo PCI, of whom 74% had non-ST-elevation ACS, and did not enroll medically-treated ACS patients. In addition, prasugrel was compared with a 300-mg loading dose of clopidogrel followed by 75-mg daily maintenance, which was the antiplatelet regimen used in the CURE study.[4-6] This regimen, which achieves a slower platelet inhibition compared with a 600-mg loading dose, was recently shown to be inferior to the double-dosing regimen examined in the CURRENT-OASIS 7 trial.[7] Post hoc analyses from TRITON-TIMI 38[2] identified two additional subgroups in whom prasugrel had no net favorable clinical benefit: patients ≥75 years of age and those <60 kg of weight.

Ticagrelor

Ticagrelor, a nonthienopyridine $P2Y_{12}$ inhibitor therapy, is a reversible agent that was shown to be superior to clopidogrel in reducing ischemic events in the PLATO trial.[8] PLATO was a landmark trial that included 18,624 medically and invasively treated ACS patients, roughly 60% of whom had non-ST-elevation ACS.[8] Using a double-blind, double-dummy design, PLATO compared ticagrelor (180-mg loading dose followed by 90 mg twice daily) with clopidogrel (300- to 600-mg loading dose followed by 75 mg daily). The primary efficacy endpoint was the time to first occurrence of the composite of vascular death, MI, or stroke. At 12 months, ticagrelor was associated with a 16% relative reduction in the primary composite outcome compared with clopidogrel, which was driven by lower rates of MI and vascular death. The benefits of ticagrelor appeared consistent across most subgroups. Importantly, ticagrelor was associated with a remarkable 1.4% absolute risk reduction in all-cause mortality (4.5% versus 5.9%; HR: 0.78; 95% CI: 0.69–0.89), and with significantly lower rates of definite stent thrombosis. There were no significant differences between the ticagrelor and clopidogrel groups in the rates of PLATO major bleeding (the primary safety endpoint), TIMI major bleeding, or fatal bleeding. However, ticagrelor was associated with a higher rate of non-CABG-related major bleeding and caused a higher incidence of dyspnea (not necessitating drug discontinuation except in a few cases) and a higher rate of ventricular pauses ≥3 seconds in the first week.

Notably, a significant interaction between treatment and the geographic region was observed, with patients enrolled in North America having no statistically significant differences between ticagrelor and clopidogrel with respect to the primary efficacy endpoint. This was attributable in subsequent analyses to possibly higher doses of aspirin used in North America.

Class I	Patients with medium/high-risk UA/NSTEMI in whom an initial invasive strategy is selected should receive dual-antiplatelet therapy. Following aspirin administration, the choice of a second antiplatelet agent at the time of PCI should be either clopidogrel, prasugrel, ticagrelor, or an intravenous GP IIb/IIIa inhibitor. (On the other hand, the choice of a second antiplatelet agent before coronary angiography should be either clopidogrel, ticagrelor, or an intravenous GP IIb/IIIa inhibitor).
	Among UA/NSTEMI patients for whom PCI is planned, a loading dose of clopidogrel 300–600 mg (given as early as possible before/at the time of PCI), prasugrel 60 mg (at the time of PCI and once coronary anatomy is defined), or ticagrelor 180 mg (given as early as possible before/at the time of PCI) should be administered.
	In UA/NSTEMI patients undergoing PCI, clopidogrel 75 mg once daily, prasugrel 10 mg once daily, or ticagrelor 90 mg twice daily should be given for at least 12 months (earlier discontinuation should be considered if bleeding risk outweighs benefits).
	Clopidogrel and ticagrelor should be withdrawn at least 5 days before planned CABG, while prasugrel should be withdrawn at least 7 days before planned CABG (unless the need for revascularization and/or the benefit of the $P2Y_{12}$ receptor inhibitors outweighs the potential bleeding risk)
Class IIa	An early invasive strategy (within 12–24 hours) is a reasonable approach in initially stabilized *high-risk* UA/NSTEMI patients.
	An invasive strategy is reasonable in patients with mild (stage II) and moderate (stage III) CKD (there is insufficient data on the benefit/risk of invasive strategy in UA/NSTEMI patients with more advanced CKD)
	After PCI, it is reasonable to use 81 mg per day of aspirin in preference to higher maintenance doses.
Class IIb	It may be reasonable to use higher clopidogrel dose (600-mg loading dose, followed by 150 mg x 6 days then 75-mg daily maintenance dose) in patients with definite UA/NSTEMI who are not at high risk for bleeding.
	If results of testing may alter management, clinicians may consider performing platelet function testing in UA/NSTEMI patients receiving $P2Y_{12}$ receptor inhibitors or genotyping for CYP2C19 pleomorphism in patients on clopidogrel therapy.
Class III	Prasugrel is harmful and should not be used in UA/NSTEMI patients with a prior history of stroke and/or TIA.
	Upstream GP IIb/IIIa inhibitors should not be used in UA/NSTEMI patients receiving aspirin and clopidogrel who are at low ischemic risk and high bleeding risk.

Table 1. Summary of important recommendations in the 2012 ACCF/AHA focused updates of the UA/NSTEMI guidelines.
UA/NSTEMI: unstable angina and non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery; CKD: chronic kidney disease.

Thus, the FDA issued a "Boxed Warning" indicating that aspirin daily maintenance doses of >100 mg decrease the effectiveness of ticagrelor. The FDA also cautioned against its use in patients with active bleeding or a history of intracranial hemorrhage and advocated a *Risk Evaluation and Mitigation Strategy*, a plan to help ensure that the benefits of ticagrelor outweigh its risks.

Ticagrelor was incorporated into the 2011 ESC guidelines for ACS,[9] which recommended the use of an oral $P2Y_{12}$ inhibitor (prasugrel or ticagrelor) as a second-line agent in preference to clopidogrel and intravenous GP IIb/IIIa inhibitors (in contradistinction to the ACCF/AHA guidelines). It is important to note that the 2012 ACCF/AAHA guidelines update did not endorse one antiplatelet over the other, but rather advocated the use of clopidogrel, prasugrel (after coronary angiography is done and patients are referred to PCI), ticagrelor, or an intravenous glycoprotein (GP) IIb/IIIa inhibitor as a second-line antiplatelet therapy that should be added to aspirin background therapy.

Higher-Dose Regimen of Clopidogrel

The guideline proposed the use of a higher-dose regimen of clopidogrel (600-mg loading dose, followed by a 150-mg daily dose for 6 days and a 75-mg daily dose thereafter) as a reasonable strategy in UA/NSTEMI patients undergoing PCI (Table I).[1] This was based on the PCI cohort substudy from the CURRENT-OASIS 7 trial, which included a total of 17,232 patients (69% of the overall CURRENT population) and in which double dosing of clopidogrel was associated with a 15% statistically significant lower 30-day composite of CV death, MI, or stroke as well as lower subacute ST rates.[6] This was, however, associated with increased major and severe bleeding (CURRENT study definition) and the need for blood transfusion. It is important to note that the findings of

this prespecified short-term subgroup analysis are derived from a larger trial that did not meet its primary outcome; there was no benefit associated with the higher-dose regimen of clopidogrel in the overall CURRENT cohort, which included PCI- and medially-managed UA/NSTEMI patients, and as such its findings should be interpreted with caution.

Role of Genotyping and Platelet Aggregation Assays

The 2012 guidelines advocated the use of platelet function testing in UA/NSTEMI patients treated with a thienopyridine or genotype testing in those treated with clopidogrel in particular, provided the results of either testing alter patients' medical management (Table 1).[1]

It is widely recognized that there is broad variability in the pharmacodynamic response to clopidogrel that is linked to several factors, including genetic polymorphisms. Clopidogrel, a prodrug, requires conversion to its active metabolite through a two-step process in the liver that involves predominantly the CYP2C19 isoenzyme (and other less important CYP450 isoenzymes). On the other hand, the prodrug prasugrel requires a single CYP-dependent step for its oxidation to the active metabolite. The presence of at least one loss-of-function allele of the CYP2C19 isoenzyme loss appears to be associated with adverse cardiovascular outcomes in at least some patients taking clopidogrel but not prasugrel.[10] In March 2010, the FDA issued a Boxed Warning to caution against the diminished effectiveness of clopidogrel in patients with an impaired ability to convert the drug to its active form,[11] outlined the options of platelet functional and/or genotype testing for patients with suspected clopidogrel resistance, but ran short of mandating the conduct of such assays. Notably, there is a paucity of clinical evidence supporting the role of either testing strategy in enhancing patients' outcomes,[9] and as such the ACCF/AHA 2012 guideline did not provide strategies for modifying therapy based on the results of these assays. The 2011 European Society of Cardiology (ESC) guidelines, on the other hand, suggested that increasing the maintenance dose of clopidogrel based on platelet function testing may be considered in selected cases.[12]

Glycoprotein IIb/IIIa Receptor Inhibitors

Findings from the landmark EARLY ACS[13] and ACUITY-Timing[14] trials influenced the UA/NSTEMI guidelines and resulted in novel recommendations for the use of glycoprotein IIb/IIIa inhibitors. EARLY ACS examined the hypothesis that a strategy of early routine administration of the GP IIb/IIIa inhibitor eptifibatide would be superior to delayed provisional administration in reducing ischemic complications among 9,492 high-risk patients with UA/NSTEMI. Early clopidogrel use was planned in 75% of the study subjects, and patients underwent PCI within 22 hours of randomization. The primary endpoint (a 30-day composite of all-cause death, MI, recurrent ischemia requiring urgent revascularization, or thrombotic bailout at 96 hours) was no different between both groups (9.3% vs. 10%, P = 0.23).[13] Although there was a nonsignificant trend favoring early GP IIb/IIIa inhibitor therapy in reducing the composite of death/MI (secondary outcome: 11.2% vs. 12.3% , P = 0.08), it was associated with an increased risk of TIMI major hemorrhage, severe or moderate bleeding (GUSTO definition), and rates of red blood cell transfusion.

Based on these findings and those of the ACUITY timing trial, the writing group recommended against the routine use of upstream GP IIb/IIIa inhibitor in ACS patients who are receiving dual antiplatelet therapy and undergoing early PCI (Table 1).[1] The writing group cautioned that the use of upstream GP IIb/IIIa inhibitors as part of triple-antiplatelet therapy for ACS may be implemented selectively, especially in high-risk patients in whom the potential antithrombotic benefits may offset the bleeding hazard (e.g., young diabetics with elevated troponin levels).

Timing of Invasive Strategy

The large-scale multicenter TIMACS trial[15] compared early (≤24 hours of randomization, median 14 hours) vs. delayed (≥36 hours, median 50 hours) angiography and intervention in patients with non–ST-segment elevation ACS. The study was terminated prematurely because of recruitment challenges (N = 3,031), and showed a nonsignificant difference in the incidence of the primary composite outcome of death, MI, or stroke (early vs. delayed; 9.6% vs. 11.3%, P = 0.15). However, early intervention reduced the secondary endpoint of death, MI, or refractory ischemia (12.9% vs. 9.5%; HR: 0.72; 95% CI: 0.58–0.89), which was driven by lower incidence of refractory ischemia.[13] In addition, patients in the highest-risk subgroup (GRACE risk score >140) experienced a 35% significant risk reduction in the incidence of the primary ischemic endpoint (21.0% vs. 13.9%, P = 0.006).[13] On the other hand, the ABOARD study[16] failed to show that a more aggressive strategy of very early intervention for non-ST-elevation ACS (analogous to the standard of primary PCI for STEMI) would lead to improved outcomes.

Based on the aforementioned findings, the 2012 UA/NSTEMI guideline update recommended early invasive strategy (within 12–24 hours) as a reasonable strategy for initially stabilized high-risk UA/NSTEMI patients.[1]

Revascularization in ACS Patients with Chronic Kidney Disease

The SWEDEHEART study[17] included a cohort of 23,262 consecutive patients hospitalized for NSTEMI in Sweden between 2003 and 2006. The study demonstrated that early revascularization within 14 days was associated with an improved 1-year mortality. After adjustment, the 1-year mortality in the overall cohort was 36% lower in NSTEMI patients who underwent early revascularization (HR: 0.64; 95% CI: 0.56–0.73; P <0.001). The improvement in 1-year mortality was similar in patients with normal estimated glomerular filtration rate and in those with mild and moderate chronic kidney disease (CKD).[17] There was no benefit observed in the subgroups of patients with stages 4 and 5 CKD; however, the latter subgroups included fewer patients and the study was underpowered to detect differences in these patients. Despite the contemporary SWEDEHEART registry limitations, including nonrandomized data and the potential for selection bias, the 2012 UA/NSTEMI guideline update recommended an early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) as a reasonable strategy in patients with mild and moderate CKD.[1]

Additional Recommendations and Controversies

The writing committee of the 2012 UA/NSTEMI guideline constructed additional evidence-based recommendations regarding measures to diminish contrast-induced nephropathy in ACS patients undergoing cardiac catheterization, including administration of adequate preparatory hydration and the calculation of the contrast volume to CrCl ratio to predict the maximum volume of contrast media that can be given safely.[1] The writing committee also emphasized the importance of standardized quality-of-care data registries to track and measure outcomes, complications, and adherence to evidence-based processes of care for ACS and endorsed the participation in these registries as a reasonable strategy.[1] The

writing committee also advocated the use of an insulin-based regimen to achieve and maintain blood glucose levels <180 mg/dL while avoiding hypoglycemia for hospitalized UA/NSTEMI patients as a reasonable approach.[18]

An important addition to the 2012 ACCF/AHA guidelines update pertains to aspirin dosing. Previously, the 2007 UA/NSTEMI guidelines endorsed medium-to-high doses of aspirin selectively, with variability in dose and duration of therapy according to the type of stent utilized. Nevertheless, the saturability of the antiplatelet effect of aspirin at low doses, the lack of dose-response relationship in studies evaluating its clinical efficacy, and the dose-dependence response of its side effects all support the use of a low dose of aspirin (e.g., the 81-mg dosage form available in the United States).[19, 20] Therefore, the 2012 ACCF/AHA guidelines update maintained that it is reasonable to use 81-mg daily aspirin in preference to higher maintenance doses after PCI (irrespective of stent type), which is concordant with the recently released 2011 ACCF/AHA PCI guidelines.[21]

The 2012 ACCF/AHA UA/NSTEMI guideline update did not provide recommendations on the use of proton pump inhibitors (PPIs) in patients on dual antiplatelet therapy (DAPT). Despite experimental and registry data suggesting diminished effectiveness of clopidogrel with the use of a PPI, the COGENT trial showed no increase in adverse cardiovascular outcomes and decreased GI bleeding from the combination of clopidogrel and omeprazole.[22] The 2012 ACCF/AHA PCI guidelines, on the other hand, recommended the use of PPIs in patients with a history of prior GI bleeding who require dual antiplatelet therapy.[21] In addition, the 2012 ACCF/AHA guideline update did address the use of anticoagulant therapies (such as the new oral factor Xa inhibitors, apixaban and rivaroxaban), anti-ischemic therapies (such as ranolazine), or new diagnostic modalities and biomarkers in patients with ACS.

Conclusions

Overall, the ACCF and AHA are to be congratulated on their continuous efforts to update the guidelines in order to critically evaluate the evidence and produce useful recommendations to guide clinicians, influence practices, and improve outcomes. One should, however, remember that only 10% of the decline in CAD mortality observed since 1986 is attributable to immediate therapies after ACS.[23] Nevertheless, acute therapies accounted for the majority of recommendations in the 2012 guideline update.[1] Finally, it is important to note that the contemporary MACE rates following ACS are in the range of 10–12% at 12–15 months,[2, 8] which highlights the alarming residual burden of morbidity and mortality in these patients.

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